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Coal Tar Phototoxicity: Characteristics of the Smarting Reaction

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We examined the properties and ultraviolet exposure parameters of tar smarts in an effort to elucidate the mechanisms involved. We showed that irradiation with 1 minimal smarting dose (MSD) of UVA immediately following tar removal lowered the MSD for 6 h, demonstrated by subsequent challenge with UVA. Following 3 MSDs this "memory" effect was demonstrable for 24 h. The smarting reaction was area dependent—smaller areas of exposure require higher doses of UVA to induce smarting. Smarting followed reciprocity over a 6-fold range of irradiances (2–12.5 mW/cm^2) but higher irradiances required higher doses of UVA, perhaps due to a delay in the recognition and reporting of smarting. The smarting reaction and delayed erythema due to UVA and tar were equally blocked by sunscreen.

In 1913, Lewin [1] was the first to recognize that coal tar products could sensitize the skin to sunlight. He described workers in contact with coal tar products who developed dermatitis and itching upon exposure to sunlight. In 1939, Foerster and Schwartz described an industrial outbreak of pitch dermatitis [2]. The photosensitivity of coal tar pitch was elegantly discussed in 1961 by Crow et al [3] who used a monochromator and determined the action spectrum of pitch phototoxicity to be in the region of 340–430 nm. Crow et al [3] noted an immediate burning or stinging sensation in subjects when tar-treated sites were exposed to UVA or sunlight, and they referred to this as the "smarting reaction." In 1968, Everett and Miller [4] established that the action spectrum for delayed erythema from 5% crude coal tar was between 350–400 nm. It has been shown that UVA plus either anthracene or crude coal tar will cause interstrand cross-linking of DNA in guinea pig skin [5]. The mediators and mechanisms involved in the production of the delayed erythema and smarting reaction to tar plus UVA have not been identified. We have examined the properties and ultraviolet exposure parameters of the smarting reaction in an attempt to help elucidate the mechanisms involved.

MATERIALS AND METHODS

Subjects

Fifty-four normal untanned adults (skin types I–III) with no history of photosensitivity served as paid volunteers. Informed consent was obtained.

UVA Light Source

Parts I and II: The Broadband UVA Portable Source (Elder) consists of a panel of 12 36-inch tubular bulbs (FS-36 T12) with irradiance at 15 cm of 6.5 mW/cm^2 for a broad spectrum of UVA (320–400 nm) as measured with the International Light IL 783 spectroradiometer. Radiation of wavelengths shorter than 313 nm made up less than 0.035% of the output (0.0023 mW/cm^2), measured using an IL grating spectroradiometer. The light source had no significant infrared emission.

Parts III and IV: A 2500-W xenon arc source (Schoeffel Instruments) with an f/1.5 quartz condensing lens system was filtered through 6 cm of a 7% $CuSO_4$ and 7% $CoSO_4$ aqueous solution and through a Schott WG 335 (1 mm) filter, then projected in a uniform (±7%) rectangular field onto the skin. By altering the projected field size, irradiance was varied between 2–50 mW/cm^2 for a broad spectrum of UVA (320–400 nm).

Tar

A single lot of 5% crude coal tar (CCT) in petrolatum was, in all experiments, applied liberally and evenly to achieve saturating conditions in designated areas of the backs of volunteers. A single lot was used because gas chromatography has shown that even crude tar received from the same supplier may vary from lot to lot [6]. One hour later, the tar was thoroughly removed with washcloth, soap (Ivory), and water, in order to minimize radiation filtering effects [7]. We have shown previously that soap and water removal of tar after a 1-h application leads to a fairly constant degree of photosensitization [8].

Sunscreen

The sunscreen used in part IV was Total Eclipse, sun protection factor (SPF) 15 (Herbert Laboratories) containing Padimate 0 (octyldimethyl PABA), octyl salicylate, and oxybenzone. Although predominantly a UVB screen, this preparation has significant absorption in the UVA region.

I. Persistence of the Smarting Reaction Following Tar Removal and the Effect of UVA Exposure Immediately Following Tar Removal on the Minimal Smarting Dose (MSD)

The 26 subjects were informed prior to testing about the photosensitizing effect of tar plus UVA in producing a burning, stinging, or smarting reaction at an unspecified time during UVA exposure. The MSD of UVA plus tar was defined as the dose of UVA required to produce the subjective sensation of smarting. The subjects were asked to signal the onset of smarting and were to report their symptoms immediately. Five percent CCT was applied to the backs of all subjects and removed 1 h later with washcloth, soap, and water. Immediately following tar removal, the back was covered except for a 1.8 × 1.8 cm aperture in an aluminum template applied to the skin. The MSD to UVA was then determined at this site.

We investigated the effect of UVA exposure immediately following tar removal on subsequent MSD determination. The back was covered except for 2 6 × 6 cm experimental sites. One of these sites was irradiated with the subject's previously determined MSD of UVA while the other site received 3 MSDs of UVA. A 6 × 6 cm self-adhesive aluminum template with 4 1.8 × 1.8 cm apertures was then applied to these sites and to a third (nonirradiated) site on the tar-treated back. The 3 sites were widely separated on different quadrants of the back. At these 3 sites (A, B, C) we determine the MSD (A) following 1 MSD of UVA, (B) following 3 MSDs of UVA, and (C) without preceding UVA irradiation at multiple time intervals after tar removal (time 0). Tar was not reapplied and we thus were measuring the persistence of the smarting reaction over time (C) as well as a "memory" of previous induction of tar smarts (A and B). A total of 6 time intervals were tested—0.5, 2, 4, 6, 24, and 30 h following tar removal. Each subject was irradiated at 4 of the 6 time intervals listed (T_1, T_2, T_3, T_4) and the MSD was simultaneously determined through an uncovered aperture at each of the 3 experimental sites (A, B, C) (see Fig 1). At least 8

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Abbreviations:
CCT: crude coal tar
MPD: minimal phototoxic dose
MSD: minimal smarting dose
SPF: sun protection factor

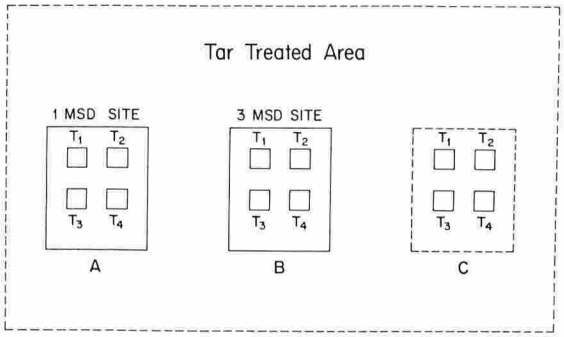

FIG 1. A schematic drawing of the experimental design in Part I. Experimental sites received (*A*) 1 MSD, (*B*) 3 MSDs, and (*C*) no immediate UVA following tar removal. The MSD was then determined within these sites at 4 time intervals following tar removal ± UVA (T_1, T_2, T_3, T_4).

subjects were tested at each time and at only 24 and 30 h were less than 10 subjects tested.

II. Area Dependence of MSD

Five percent CCT was applied to the backs of 13 subjects and thoroughly removed 1 h later with washcloth, soap, and water. Adhesive aluminum templates with square apertures of different areas were then applied to the back and all other areas were covered. Squares tested were (1) 0.45 cm; (2) 0.9 cm; (3) 1.8 cm; (4) 3.6 cm; (5) 7.2 cm; and (6) 14.3 cm across. The MSD for each size aperture was determined in random order. The subjects' MPD to UVA on tar-treated skin was also determined using UVA exposure doses of 1–17 J/cm^2 (2.5–43 min). The MPD was defined as the minimal dose of UVA causing 1+ erythema on tar-treated skin with distinct borders read at 24 h after exposure.

III. Irradiance Dependence of MSD

Five percent CCT was applied to the backs of 8 subjects and thoroughly removed 1 h later with a wash cloth, soap, and water. Immediately following tar removal a 4.5 × 4.5 cm aperture in an aluminum template applied to the back was irradiated with UVA at separate sites with the following irradiances: (1) 2 mW/cm^2; (2) 6 mW/cm^2; (3) 12.5 mW/cm^2; (4) 25 mW/cm^2; and (5) 50 mW/cm^2. Each subject was exposed to all 6 irradiances in random order and the MSD was determined.

IV. Effect of Sunscreen on MSD

Five percent CCT was applied to the forearm of 7 volunteers and removed 1 h later with a washcloth, soap, and water. Immediately following tar removal a thin layer of sunscreen (Total Eclipse SPF 15) was applied to the area for 30 min. An aluminum template with a 1.8 × 1.8 cm aperture was applied to this area and the MSD was determined at this site. This was repeated at 2 other sites on the forearm. The mean MSD for these 3 determinations was calculated. After a similar application of tar and sunscreen, the MPD of UVA was measured using UVA exposure doses of 1.5–35.25 J/cm^2 (4–90 min). Identical determinations were performed on the opposite forearm, i.e., MSD at 3 sites plus MPD, but without sunscreen. Since sunscreen had been applied for 30 min following tar removal on the other forearm, UVA irradiation was delayed for 30 min after tar removal.

Statistical Analysis

Student's *t*-test was used to compare sample means between 2 samples, and analysis of variance was used to test differences in means among multiple samples. Linear (least squares) regression analysis was used to study the relation between variables.

RESULTS

I. Persistence of the Smarting Reaction Following Tar Removal and the Effect of UVA Exposure Immediately Following Tar Removal on the MSD

After a single application of tar and thorough washing, susceptibility to the smarting reaction persisted for 30 h in all cases. As noted in Fig 2, the MSD significantly increased with

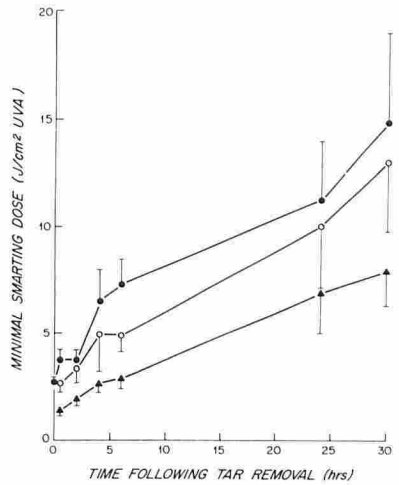

FIG 2. The MSD was determined following 1 MSD (○——○), 3 MSDs (▲——▲), and without preceding UVA irradiation (●——●). N = 26 for time 0, 30 min; N = 17 for 2 h; N = 10 for 4 h; N = 19 for 6 h; N = 9 for 24 h and 30 h. *Vertical bars* represent SEM.

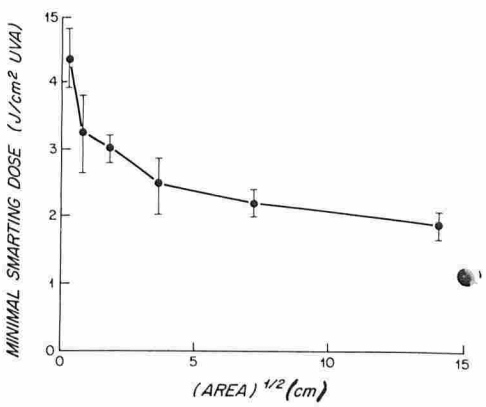

FIG 3. The MSD was determined using multiple areas of exposure ranging in size from 0.45 × 0.45 cm to 14.3 × 14.3 cm. N = 13. *Vertical bars* represent SEM.

increasing intervals between tar removal and UVA exposure ($p < 0.001$). Compared to sites irradiated only once with UVA, the MSD at sites that had received 3 MSDs previously was significantly lower at all times tested, up to 24 h. After 1 MSD, on the other hand, the memory effect was smaller, with statistically significant lowering of MSD only at 30 min ($p < 0.04$) and at 6 h ($p = 0.0005$).

On some occasions the smarting reaction was accompanied by an immediate erythema which faded in several hours; however, this was not a consistent finding with 1 MSD of UVA. No urticarial response was noted at this dose. Three MSDs of UVA produced an immediate wheal and flare in all patients.

II. Area Dependence of MSD

As shown in Fig 3, the MSD decreases as the irradiated area increases. The trend was highly significant ($p < 0.00001$). With increases of area beyond 3.6 × 3.6 cm, the decreases in MSD are less marked.

III. Irradiance Dependence of MSD

Over a wide range of irradiances (2–12.5 mW/cm^2) there was no significant difference in MSD (see Fig 4). At higher irradiances, 25 and 50 mW/cm^2, the MSD was found to be significantly higher ($p \leq 0.05$). There was no significant difference between the MSDs at 25 and 50 mW/cm^2 ($p = 0.1$).

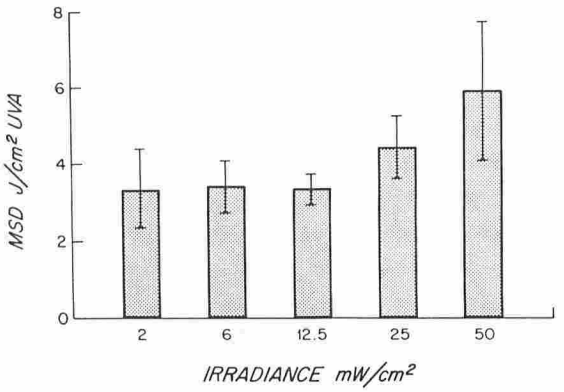

FIG 4. The MSD was measured at multiple irradiances of UVA ranging from 2 mW/cm² to 50 mW/cm². A significantly increased MSD was noted with the highest irradiances tested, 25 and 50 mW/cm² ($p < 0.05$). N = 8. *Vertical bars* represent SEM.

TABLE I. *Effect of sunscreen on minimal smarting dose*

MPD J/cm² (N = 6)		*MSD J/cm² (N = 7)*	
With sunscreen	19.7 ± 6.6	With sunscreen	5.06 ± 1.49
(range 14–30.9)		(range 2.99–7.10)	
Without sunscreen	10.7 ± 5.2	Without sunscreen	2.78 ± 0.66
(range 7.5–19.6)		(range 1.92–3.36)	
Ratio		*Ratio*	
1.94 ± 0.31		1.81 ± 0.23	
(range 1.58–2.27)		(range 1.56–2.15)	

Minimal phototoxic dose (MPD) and minimal smarting dose (MSD) were determined with and without the presence of sunscreen (Total Eclipse SPF 15). Sunscreen was equally effective in inhibiting both delayed erythema and the immediate smarting reaction. Values for MPD, MSD, and their ratios are listed ± SD.

IV. Effect of Sunscreen on MSD

The results are listed in Table I. There was a significant difference between the MSDs with and without sunscreen ($p < 0.001$). Similarly there was a significant difference between the MPDs with and without sunscreen, ($p < 0.0002$). The ratios comparing MSD and MPD with and without sunscreen (1.81 vs 1.94) were not significantly different. ($p > 0.15$).

DISCUSSION

In 1977, Kaidbey and Kligman [9] studied the phototoxic reaction to tar in detail and described it as a two-stage process: an immediate wheal followed 24 h later by a delayed response. With continued UVA exposure, an immediate smarting sensation preceded an immediate erythema which then developed into the wheal and flare. The smarting sensation would dissipate within minutes of stopping UVA exposure while the wheal would resolve in 30–60 min.

In a separate study we examined the kinetics and exposure parameters of coal tar phototoxicity [8]. We demonstrated a rather pronounced, constant decrease in phototoxicity when subjects were irradiated at increasing intervals of time following tar removal. The MPD and MSD showed a similar, roughly parallel, time dependence. The sensitivity to the smarting reaction remained greater than the sensitivity for delayed erythema (MSD < MPD) at all times tested, yet even 30 h after a single 1-h application of 5% CCT, photosensitivity persisted as demonstrated by smarting and erythema [8].

In the present study, we further examined the properties and ultraviolet exposure parameters of the smarting reaction to UVA plus CCT in an effort to elucidate the mechanisms of this interesting aspect of coal tar phototoxicity. We showed that irradiation with 1 MSD of UVA immediately following tar removal significantly lowered the MSD for 6 h, compared with sites not immediately irradiated, as demonstrated by subsequent challenge with UVA. Following 3 MSDs the effect was demonstrable for 24 h (Fig 2). Due to this "memory" effect we speculate that a slowly repaired, UVA-induced photoproduct is formed and persists for some time, leading to a lowered threshold upon reexposure.

UV radiation at high irradiances produces an immediate burning sensation due to nonspecific, rapid heating of the skin [10]. In our study we showed that the smarting reaction is area dependent—smaller areas of exposure require higher doses of UVA to induce smarting (Fig 3). The area dependence of smarting would be consistent with a role for thermal effects—thermal transfer properties cause an area dependence secondary to relative edge losses and blood flow. But one might also postulate that an accumulating photoproduct must stimulate a sufficient number of susceptible nerve endings before smarting will be noted.

We varied the irradiance of UVA exposure and determined its effect on MSD. The principle of reciprocity assures that a given exposure dose yields a constant biologic response—doubling the irradiance may be compensated for by halving the exposure time [9–11]. Photobiologic responses that follow reciprocity may be assumed to derive from a photochemical reaction. Over a 6-fold range of irradiances (2–12.5 mW/cm²), the smarting reaction obeys reciprocity and appears not to be flux dependent. With much higher irradiances (25 and 50 mW/cm²) the dose of UVA necessary to induce smarting is significantly higher ($p < 0.05$) (Fig 4). This may represent a finite lag time before smarting will be recognized and reported by the subject. If thermal mechanisms were involved one would expect more rapid onset of smarting (lowered MSD) at higher irradiances.

We measured two manifestations of coal tar phototoxicity—delayed erythema (MPD) and the smarting reaction (MSD), and showed that they were equally affected by the application of sunscreen (Total Eclipse SPF 15) prior to UVA irradiation (Table I). The action spectrum for delayed erythema and smarting have both been demonstrated to lie within the UVA range [3,4]. The ability to equally block both aspects of tar photosensitization suggests that photochemical, rather than thermal, mechanisms are responsible for both.

The mechanisms underlying coal tar phototoxicity are not completely understood. Pathak and Biswas [5] demonstrated that UVA plus either CCT or anthracene caused interstrand cross-linking of DNA in guinea pig skin. There is evidence that coal tars alone directly suppress epidermal DNA synthesis in the hairless mouse [12,13].

Other mechanisms of coal tar phototoxicity have been considered. Anthracene, a photosensitizer in coal tar, has been shown to localize in lysosomal membranes [15]. Subsequent irradiation with UVA caused increased permeability and cell death. Allison et al [16] showed that some photosensitizers are readily taken up by lysosomes of mast cells and endothelial cells. Due to the immediate urticarial response noted with tar and sufficient doses of UVA, two groups studied the use of antihistamines in blocking coal tar phototoxicity. Crow et al [3] found no effect of oral antihistamines in preventing smarting, erythema, or urticaria. Similarly, Kaidbey and Kligman [9] could show no significant effects with oral and local antihistamines.

Both Crow et al [3] and Kaidbey and Kligman [9] demonstrated that arterial occlusion abolished all phases of coal tar phototoxicity—smarting, erythema, and urticaria. They concluded that coal tar photosensitization was due to photodynamic (photo-oxidative) reactions. Joshi and Pathak [21] recently presented evidence of the production of reactive cytotoxic species of oxygen (singlet oxygen, $^1O_2$) in vitro when CCT was irradiated with UVA. Further studies are necessary to document the production of singlet oxygen in vivo in response

to CCT plus UVA; the role of singlet oxygen in the smarting reaction merits further investigation.

Although UVA-induced coal tar photosensitization can be effective in treatment of generalized psoriasis, treatment times are long and treatment must be frequently interrupted to obtain relief from the smarting reaction [22]. We have previously demonstrated that the MSD is lower than the MPD at all times tested [9]. The area dependence of smarting determines that total-body exposure to UVA would induce smarting at even lower doses. Our present study also demonstrates that utilizing UVA at a lower irradiance would not avoid the smarting reaction. In addition, previous exposure to UVA would result in an increased sensitivity to smarting. These factors are further evidence for the impracticality of UVA plus tar in the treatment of psoriasis. The failure of psoriasis patients treated with the Goeckerman regimen [23,24] to complain of smarting confirms the inability of UV sources currently used to deliver sufficient UVA to induce coal tar phototoxicity [25,26].

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